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A phase I and pharmacologic study of Belotecan in combination with Cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer

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Background: Belotecan (Camtobell®; CKD602) is a novel camptothecin derivative antitumor agent. This phase I study was designed to determine the maximum-tolerated dose (MTD), toxicity profile, and dose-limiting toxicity (DLT) of belotecan in combination with cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer (ED SCLC). Furthermore, pharmacokinetics (PK) and preliminary antitumor activity of belotecan against SCLC were evaluated.

Methods: Patients with ED SCLC, age 18-70, ECOG PS 0-2, no prior chemotherapy and adequate organ function were eligible. Cisplatin with fixed dose of 60 mg/m^2 was administered intravenously (i.v.) over 2 hours on day 1. Belotecan was administered iv as intermittent 30-minute infusions on days 1 to 4, starting dose of 0.40 mg/m^2/day with increment of 0.05 mg/m^2/day. Modified Fibonacci escalation was used (3 to 6 patients per cohort) and intra-patient dose escalation was not allowed. PK of belotecan was determined during the first treatment using non-compartmental pharmacokinetic analysis.

Results: Seventeen patients were treated at 4 dose levels (0.40 to 0.55 mg/m^2/day). At 0.55 mg/m^2/day of belotecan, the DLT of grade 4 neutropenia with fever occurred in 2 of 5 patients, and therefore the MTD was 0.50 mg/m^2/day. Interestingly, out of 17 patients, there were 14 partial responses (82.4%; 95% CI, 63.4% to 100.0%). PK analysis revealed that at 0.50 mg/m^2/day, plasma clearance of belotecan was 5.78 ± 1.32 L/hr and terminal half-life was 8.55 ± 2.12 hr. Fraction of excreted amount in urine was 37.36 ± 5.55 %. PK of belotecan were not altered by administration of cisplatin, as compared with historical control.

Conclusions: The MTD of belotecan was 0.50 mg/m^2/day for intermittent 30-min i.v. infusion for 4 days in combination with cisplatin 60 mg/m^2 on day 1 every 3 weeks. Furthermore, very promising antitumor activity against SCLC was observed. The phase II study is being conducted now.

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Randomized trial of a 3-fold dose intensification of Ifosfamide, Carboplatin, Etoposide chemotherapy for the treatment of small cell lung cancer

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Purpose: Early high-dose chemotherapy was tested in different non-randomized trials with impressive complete response rate, and over the years this approach continued to be proposed without the possibility to obtain firm conclusions, but in submitting cohorts of patients to significant toxicities. The early administration of multiple and sequential high-dose chemotherapy supported by peripheral blood progenitors allowed to increase the dose intensity of chemotherapy by three fold. The EBMT carried out a randomized trial to test the impact of such an intensification on long-term survival of patients with small cell lung cancer.

Methods: Patients with limited and extensive disease with ≤2 metastatic sites were randomized to 6 cycles of standard dose ICE (ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, and etoposide 360 mg/m^2 over 2 days every 28 days) or 3 cycles of high-dose ICE (ifosfamide 10 g/m^2, carboplatin AUC 20, etoposide 1200 mg/m^2, all drugs divided over 4 days, every 28 days) supported by PBPCs previously collected following 2 cycles of epidoxorubicin 150 mg/m^2 and paclitaxel 175 mg/m^2 and filgrastim. Due to a low accrual rate an interim analysis was carried out with strong boundaries that allowed to close the trial prematurely and to obtain firm and final conclusions.

Results: The median relative dose intensity of the high-dose ICE was 293% (174% to 392%) compared to the standard ICE. The 3- year survival rate was 18% and 19% in the high-dose and standard dose arm respectively. The median survival rate were not statistically different(18.1 months and 14.4 months), neither the overall (78% and 68%) and complete response rate (39% and 34%). An analysis according to stratification factors (limited vs extensive disease, LDH normal vs abnormal, male vs female, PS 0 vs 1) could not disclose any subgroups that benefited from the intensive strategy. Hematological toxicity was significant in the standard arm (grade >3 neutropenia 70%, anemia 25%, thrombopenia 25%) associated with a toxic death rate at 4%. In the high-dose arm, beside the expected severe myelosuppression, the toxic death rate was at 10% and the median hospitalization time was 20 days compared to 4 days for the standard treatment.

Conclusions: Despite an increase in the peak dose, the total dose and the dose-intensity by 3 fold ICE chemotherapy did not improve the long term outcome of SCLC but was toxic and expensive. This stategy should be abandoned.

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Activity and feasibility of biweekly carboplatin (Cb) plus Gemcitabine (G) as first line treatment in small cell lung cancer (SCLC) with extensive disease (ED)

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Background: Standard treatment for ED achieves a median suvival time of 9 months with only 1-2% of long survivors. Biweekly schedules have demostrated to be convenient for patients (pts) with different cancers. We assessed the eficacy and toxicity of a biweekly combination of Cb and G in chemonaïve pts.

Methods: We included pts with ED or limited disease unfit for combined radical radiotherapy with ECOG PS 0-2. Pts with brain metastasis were also enrolled. Treatment consisted of: Cb AUC 3 day 1 and G 2000 mg/m^2 day 1 every 14 days, final response was assessed after 8 cycles